B28

PATENT SPECIFICATION

(11) 1 474 296

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(21) Application No. 2924/75 (22) Filed 23 Jan. 1975
(61) Patent of addition to No. 1416872 dated 22 Feb. 1973
(23) Complete Specification filed 23 Jan. 1976
(44) Complete Specification published 18 May 1977
(51) INT CL² C07D 215/44 A61K 31/435 C07D 401/12 (C07D 401/12 211/32 211/56 215/44)
(52) Index at acceptance
C2C 1532 1534 213 215 220 226 22Y 250 251 25Y 280 281 28X 29X 29Y 313 316 31Y 322 323 32Y 337 339 342 34Y 351 355 35X 366 440 584 604 620 625 628 62X 630 650 660 665 668 670 675 699 790 79Y KJ LL LS

(72) Inventors JOHN LEHEUP ARCHIBALD, JOHN TERENCE ARNOTT BOYLE and JOHN CHRISTOPHER SAUNDERS

(19)

(54) 4-AMINOQUINOLINE DERIVATIVES

PATENTS ACT 1949

SPECIFICATION NO 1474296

The following corrections were allowed under Section 76 on 23 May 1978.

Page 1, line 19, *after* where *delete* R^1 *insert* R^2

THE PATENT OFFICE
20 June 1978

Bas 49146/4

X ~ N (I)

and their acid addition salts, where X is halogen atom or a trifluoromethyl group; Z is hydrogen, halogen, trifluoromethyl, lower alkyl, lower alkoxy, hydroxyl, nitro, amino or mono- or di-alkyl substituted amino; R^1 represents hydrogen or lower alkyl; and R^2 represents [mono(lower alkyl)amino](lower alkyl), [di(lower alkyl)amino](lower alkyl), piperidyl, 1-[ar(lower)alkyl]-piperidyl or 1-(lower alkyl)piperidyl or $-NR^1R^2$ represents [mono (lower alkyl) amino]piperidino or [di(lower alkyl)amino]piperidino, preferably R^2 represents [di(lower alkyl) amino](lower alkyl) or 1-(lower alkyl)piperidyl or $-NR^1R^2$ represents [di(lower alkyl)amino]piperidino. We particularly prefer those compounds where R^2 is [di(lower alkyl)amino](lower alkyl) whilst R^1 is lower alkyl and those where R^1 is 1-(lower alkyl)piperidyl.

The term "lower" as used herein in connection with such groups as "alkyl" or "alkoxy" denotes that the group contains up to 6 carbon atoms, preferably up to 4 carbon atoms. By the term "ar(lower)alkyl" there is meant lower alkyl substituted by aryl. The aryl group may be unsubstituted or substituted with one or more substituents conventionally used in medicinal chemistry. Preferably the aryl group is phenyl.

It will be apparent to those skilled in the art that the above definition of R^2 includes moities possessing an asymmetric carbon atom, especially for instance, in the cases where R^2 represents a 1-[ar(lower)alkyl]-3-piperidyl or 1-(lower alkyl)-3-piperidyl group. It is to be understood that general formula I is intended to encompass both enantiomers where the compound contains an asymmetric carbon atom and mixtures of the enantiomers, for instance, a racemic mixture of the enantiomers. General methods are recorded in the literature for the resolution of enantiomers.

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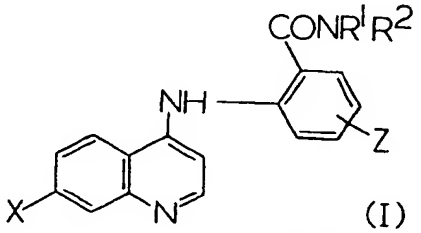
(72) Inventors JOHN LEHEUP ARCHIBALD, JOHN TERENCE ARNOTT BOYLE and JOHN CHRISTOPHER SAUNDERS

(54) 4-AMINOQUINOLINE DERIVATIVES

(71) We, JOHN WYETH & BROTHER LIMITED, of Huntercombe Lane South, Taplow, Maidenhead, Berkshire, a British Company, do hereby declare the invention, for which we pray that a patent may be granted to us and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention concerns now 4-amino-quinoline derivatives, a process for their preparation and pharmaceutical compositions containing them.

The invention provides new 4-aminoquinoline derivatives of the general formula



(I)

and their acid addition salts, where X is halogen atom or a trifluoromethyl group; Z is hydrogen, halogen, trifluoromethyl, lower alkyl, lower alkoxy, hydroxyl, nitro, amino or mono- or di-alkyl substituted amino; R^1 represents hydrogen or lower alkyl; and R^2 represents [mono(lower alkyl)amino](lower alkyl), [di(lower alkyl)amino] (lower alkyl), piperidyl, 1-[ar(lower)alkyl]-piperidyl or 1-(lower alkyl)piperidyl or $-NR^1R^2$ represents [mono (lower alkyl) amino]piperidino or [di(lower alkyl)amino]piperidino, preferably R^2 represents [di(lower alkyl) amino](lower alkyl) or 1-(lower alkyl)piperidyl or $-NR^1R^2$ represents [di(lower alkyl)amino]piperidino. We particularly prefer those compounds where R^2 is [di(lower alkyl)amino](lower alkyl) whilst R^1 is lower alkyl and those where R^1 is 1-(lower alkyl)piperidyl.

The term "lower" as used herein in connection with such groups as "alkyl" or "alkoxy" denotes that the group contains up to 6 carbon atoms, preferably up to 4 carbon atoms. By the term "ar(lower)alkyl" there is meant lower alkyl substituted by aryl. The aryl group may be unsubstituted or substituted with one or more substituents conventionally used in medicinal chemistry. Preferably the aryl group is phenyl.

It will be apparent to those skilled in the art that the above definition of R^2 includes moities possessing an asymmetric carbon atom, especially for instance, in the cases where R^2 represents a 1-[ar(lower)alkyl]-3-piperidyl or 1-(lower alkyl)-3-piperidyl group. It is to be understood that general formula I is intended to encompass both enantiomers where the compound contains an asymmetric carbon atom and mixtures of the enantiomers, for instance, a racemic mixture of the enantiomers. General methods are recorded in the literature for the resolution of enantiomers.

SEE ERRATA SLIP ATTACHED

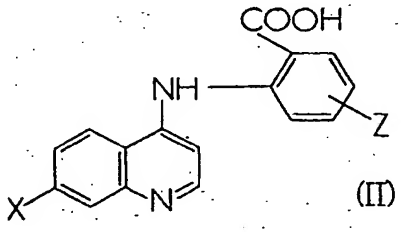
In the compounds of the invention, X preferably represents a halogen atom, for example, a chlorine or bromine atom, but may also represent a trifluoromethyl group. Illustrative meanings of Z include hydrogen, chlorine, bromine atoms and trifluoromethyl, lower alkyl or alkoxy (for example, methyl, ethyl, propyl, butyl, methoxy, ethoxy, propoxy and butoxy), hydroxyl, nitro, amino, methylamino, ethylamino, dimethylamino and diethylamino groups. Z is preferably hydrogen.

As illustrative meanings of R^1 there may be mentioned hydrogen, methyl, ethyl, propyl, butyl and hexyl. As illustrative meanings of [mono(lower alkyl)amino](lower alkyl) there may be mentioned (methylamino)methyl and (ethylamino)ethyl. As illustrative meanings of [di(lower alkyl)amino](lower alkyl) there may be mentioned [di-(methyl)amino]methyl, [di(ethyl)-amino]ethyl, [N-methyl-N-ethylamino]propyl, [di-(ethyl)amino]butyl and [di(butyl)amino]ethyl. Piperidyl may be 3-piperidyl or 4-piperidyl. As illustrative meanings of 1-(lower alkyl)piperidyl there may be mentioned 1-ethyl-2-piperidyl, 1-ethyl-3-piperidyl, 1-ethyl-4-piperidyl, 1-methyl-4-piperidyl, 1-methyl-3-piperidyl, 1-propyl-3-piperidyl, 1-butyl-4-piperidyl and 1-pentyl-3-piperidyl. As illustrative meanings of 1-[ar(lower) alkyl]piperidyl there may be mentioned 1-benzyl-3-piperidyl, 1-benzyl-4-piperidyl, 1-phenethyl-3-piperidyl and 1-phenethyl-4-piperidyl. As illustrative meanings of [di(lower alkyl)amino]piperidino and [mono-(lower alkyl)amino]piperidino there may be mentioned 4-(dimethylamino)piperidino, and 3-(dibutylamino)-piperidino, 4-(methylamino)piperidino and 3-(ethylamino)-piperidino.

Examples of acid addition salts are those formed from inorganic and organic acids and in particular pharmaceutically acceptable acid addition salts such as the sulphate, hydrochloride, hydrobromide, hydroiodide, nitrate, phosphate, sulphonate (such as the methanesulphonate and *p*-toluene-sulphonate), acetate, maleate, fumarate, tartrate, malonate, citrate and formate.

The compounds of the invention may be made by building the compound up by known reactions. In particular the amide linkage shown in formula I as —$CONR^1R^2$ may be formed by acylation of an appropriate amine, and a primary amino-substituted benzamide may be converted to the secondary amine by introducing the 7-(halo or trifluoromethyl)-4-quinolyl group in known manner.

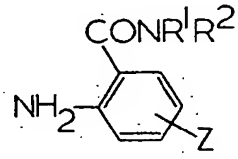
The invention provides a method of making compounds of the formula I and their acid addition salts, wherein (a) a compound of the formula HNR^1R^2 where R^1 and R^2 are defined in connection with formula I, or a corresponding compound with an activated amino group, is acylated with a compound of formula (II)



(II)

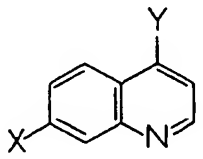
(wherein X and Z are as defined above in connection with formula I), or a corresponding compound with a protecting group, or a reactive derivative of the compound of formula (II) or its corresponding compound with a protecting group;

or (b) a compound of the formula (III)



(III)

(where R^1, R^2 and Z are as defined in connection with formula I) or a corresponding compound with a protecting group, is reacted with a compound of formula (IV)



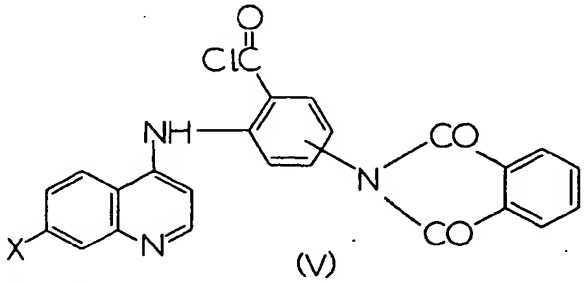
(IV)

(where X is as defined above in connection with formula I and Y denotes a group or atom replaceable by nucleophilic attack by compound of formula III). Y is for example, an iodine atom, a bromine atom or a chlorine atom or an organosulphonyloxy group, for instance, *p*-toluenesulphonyloxy. Where necessary or if desired, the process may also include removal of a protecting group and, if desired, conversion of a free base form of compound of formula I into an acid addition salt form or conversion of an acid addition salt form of a compound of formula I into the corresponding free base form.

Starting materials of formula HNR^1R^2 and formulae II, III and IV are known compounds or, if new, are accessible by conventional methods.

The acylation method may be carried out by reacting the compound of formula II with the compound of formula HNR^1R^2 or a corresponding compound with a protecting group, in the presence of a condensing agent, for instance, a carbodiimide. Alternatively the acid of formula II may be reacted with a compound of formula $Q—R^2$ where Q is an activated amino group. The amino group may be activated for example, by forming the phosphazo derivative. The reactive acylating derivatives of the compound of formula II may be employed, for example, active esters, acyl halides, simple or mixed anhydrides and the acid azide. The acid halides, particularly the acid chloride are especially suitable. Preferably the compound of formula HNR^1R^2 is acylated with a reactive derivative of the acid of formula II.

The acylation product may be recovered from the reaction mixture by standard isolation procedures. Acylating derivatives of the acid of formula II may include protection for a group Z sensitive to acylation. For example, a final product in which Z is an amino function can be formed by using an acylating derivative of the acid of formula



(V)

and converting the phthalimido group to an $—NH_2$ group by reaction with hydrazine. The new compounds of the invention are normally quite stable to hydrolysis under acid conditions and therefore favour protecting groups that are readily hydrolysed off under acid conditions.

Compounds of the formula III are accessible in standard manner, for example, by acylation of a compound of formula NHR^1R^2 where R^1 and R^2 have the meanings given in connection with formula I with an acylating derivative of an *o*-nitrobenzoic acid or 2-(protected amino) benzoic acid and subsequent reduction of the nitro group or removal of the amino protecting group. The reaction of the primary amine III with the compound of formula IV may be carried out in conventional manner for amination of 4-substituted quinolines. The reaction products may be recovered from the reaction mixtures by standard isolation procedures. In certain cases it is expedient to incorporate a protecting group for amino in the compound of formula III to reduce or preclude undesired reaction of the compounds of formula IV with an amino function as Z. The protected amino group may be a phthalimido group. In such cases the protecting group is removed after the reaction with the compound of formula IV.

The compounds of the present invention may be isolated in free base form or as acid addition salts. Acid addition salts may be converted into the free bases in conventional manner. The free base forms may be converted into acid addition salts in conventional manner, for instance, by adding ethereal hydrogen chloride to a solution of the free base where a hydrochloride salt is desired.

The compounds of the present invention are indicated for pharmacological usage and, in particular, generally demonstrate anti-inflammatory activity. A literature reference for testing for anti-inflammatory activity is Newbould, B.B., Brit. Jour. Pharm. Chemoth., *21*: 127—136 (1963). Some of the new compounds of the invention also show anti-hypersensitive activity. 2-(7-chloro-4-quinolylamino)-N-(2-diethylaminoethyl)-N-ethylbenzamide demonstrates activity as a blood platelet aggregation inhibitor.

The invention also includes pharmaceutical compositions containing as active ingredients a compound of formula (I) or a pharmaceutically acceptable acid addition salt thereof, which may be micronised if desired. In addition to the active ingredient, said compositions also contain a non-toxic carrier. Any suitable carrier known in the art can be used to prepare the pharmaceutical compositions. In such a composition, the carrier may be a solid, liquid or mixture of a solid and a liquid. Solid form compositions include powders, tablets and capsules. A solid carrier can be one or more substances which may also act as flavouring agents, lubricants, solubilizers, suspending agents, binders, or tablet-disintegrating agents; it can also be an encapsulating material. In powders the carrier is a finely divided solid which is in admixture with the finely divided active ingredient.

In tablets the active ingredient is mixed with a carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain from 5 to 99, preferably 10—80% of the active ingredient. Suitable solid carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, a low melting wax, and cocoa butter. The term "composition" is intended to include the formation of an active ingredient with encapsulating material as carrier to give a capsule in which the active ingredient (with or without other carriers) is surrounded by carrier, which is thus in association with it. Similarly cachets are included.

Sterile liquid form compositions include sterile solutions, suspensions, emulsions, syrups and elixirs. The active ingredient can be dissolved or suspended in a pharmaceutically acceptable sterile liquid carrier, such as sterile water, sterile organic solvent or a mixture of both. Preferably a liquid carier is one suitable for parenteral injection. Where the active ingredient is sufficiently soluble it can be dissolved in normal saline as a carrier; if it is too insoluble for this it can often be dissolved in a suitable organic solvent, for instance aqueous propylene glycol or polyethylene glycol solutions. Aqueous propylene glycol containing from 10 to 75% of the glycol by weight is generally suitable.

In other instances compositions can be made by dispersing the finely-divided active ingredient in aqueous starch or sodium carboxymethyl cellulose solution, or in a suitable oil, for instance arachis oil. Liquid pharmaceutical compositions which are sterile or suspensions can be utilised by intramuscular, intraperitoneal or subcutaneous injection. In many instances a compound is orally active and can be administered orally either in liquid or solid composition form.

Preferably the pharmaceutical composition is in unit dosage form. In such form, the composition is sub-divided in unit doses containing appropriate quantities of the active ingredient; the unit dosage form can be a packaged composition, the package containing specific quantities of compositions, for example packeted powders or vials or ampoules. The unit dosage form can be a capsule, cachet or tablet itself, or it can be the appropriate number of any of these in package form.

The quantity of active ingredient in a unit dose of composition may be varied or adjusted from 5 mg. or less to 500 or more, according to the particular need and the activity of the active ingredient. The invention also includes the compounds in the absence of carrier where the compounds are in unit dosage form.

The invention is illustrated by the following Examples:—

EXAMPLE 1

2-(7-Chloro-4-quinolylamino)-N-(1-ethyl-3-piperidyl)benzamide

A solution of 10.05 grams of 2-(7-chloro-4-quinolylamino) benzoic acid hydrochloride in 60 millilitres of thionyl chloride was refluxed for two hours. After evaporation of the thionyl chloride 50 millilitres of benzene were added and the mixture re-evaporated to give the acid chloride as a pinkish solid. This was then added in

portions to a stirred, ice-cooled solution of 3.84 grams of 3-amino-1-ethyl-piperidine in 60 millilitres of chloroform with 80 millilitres of water and 31.8 grams of sodium carbonate. After the addition was complete the mixture was stirred at room temperature overnight, filtered and the filtrate (chloroform-water) separated, the aqueous layer further extracted with chloroform, the chloroform extracts combined, dried over magnesium sulphate and evaporated to give a brown gum.

Trituration with n-hexane gave 8.9 grams of the title compound as the hemihydrate.

Melting point:	187—188°C	
Analysis:	Found	C, 66.5%; H, 6.23%; N, 13.4%
		$C_{28}H_{25}ClN_4O \cdot \frac{1}{2}H_2O$
requires		C, 66.1%; H, 6.27%; N, 13.4%.

EXAMPLE 2

2-(7-Chloro-4-quinolylamino)-N-(2-diethylaminoethyl)-N-ethylbenzamide.

A solution of 10.05 grams of 2-(7-chloro-4-quinolylamino) benzoic acid hydrochloride in 60 millilitres of thionyl chloride was refluxed for two hours. After evaporation of the thionyl chloride 50 millilitres of benzene were added and the mixture re-evaporated to give the acid chloride as a yellowish solid. This was then added in portions to a stirred, ice-cooled solution of 4.33 grams of N,N,N¹-triethylethylenediamine in 60 millilitres of chloroform with 100 millilitres of water and 31.8 grams of sodium carbonate. After the addition was complete the mixture was stirred at room temperature overnight, filtered and the filtrate (chloroform-water) separated, the aqueous layer further extracted with chloroform, the chloroform extracts combined, dried over magnesium sulphate and evaporated to give 16 grams of a brown gum. This was dissolved in 250 millilitres of ether and ethereal hydrogen chloride added to precipitate 14.4 grams of the title compound as the hydrochloride dihydrate.

Melting point:	155°C	
Analysis:	Found	C, 54.0%; H, 6.30%; N, 10.2%
		$C_{24}H_{29}ClN_4O \cdot 2HCl \cdot 2H_2O$
requires		C, 54.0%; H, 6.61%; N, 10.5%.

EXAMPLE 3

2-(7-Chloro-4-quinolylamino)-N-(2-diethylaminoethyl)benzamide

A solution of 6.7 grams of 2-(7-chloro-4-quinolylamino) benzoic acid hydrochloride in 40 millilitres of thionyl chloride was refluxed for two hours. After evaporation of the thionyl chloride 50 millilitres of benzene were added and the mixture re-evaporated to give the acid chloride as a pinkish solid. This was then added in portions to a stirred, ice-cooled solution of 2.32 grams of N,N-diethylethylenediamine in 40 millilitres of chloroform with 100 millilitres of water and 21.2 grams of sodium carbonate. After the addition was complete the mixture was stirred at room temperature overnight, filtered and the filtrate (chloroform-water) separated, the aqueous layer further extracted with chloroform, the chloroform extracts combined, dried over magnesium sulphate and evaporated to give an oil. This was dissolved in 200 millilitres of ether and ethereal hydrogen chloride added to precipitate 7.4 grams of the title compound as the dihydrochloride hydrate.

Melting point:	225°C.	
Analysis:	Found	C, 51.2%; H, 5.99%; N, 10.6%
		$C_{22}H_{25}ClN_4O \cdot 2HCl \cdot 2\frac{1}{2}H_2O$
requires		C, 51.3%; H, 6.26%; N, 10.9%

EXAMPLE 4

1-[2-(7-chloro-4-quinolylamino)-benzoyl]-4-dimethylaminopiperidine

A solution of 8 grams (0.024 mole) of 2-(7-chloro-4-quinolylamino)-benzoic acid hydrochloride in 60 millilitres of thionyl chloride was refluxed for two hours. Evaporation followed by the addition of dry benzene (2×50 ml) and re-evaporation gave the acid chloride as a pinkish solid. This was added in portions to a stirred, ice-cooled solution of 4.8 grams (0.0239 mole) of 4-dimethylamino piperidine dihydrochloride in 60 millilitres of chloroform with 100 millilitres of water and 31.8 grams of sodium carbonate. The mixture was stirred at room temperature overnight. The mixture was then filtered, the filtrate was separated and the chloroform layer was evaporated to give an oil. The oil was converted to the hydrochloride in isopropyl

alcohol-ether. This was dissolved in water and saturated sodium carbonate solution added to precipitate the free base as a yellow solid. Reconversion to the hydrochloride and back to the free base again gave 2.5 grams of title compound as a hemihydrate.

Melting point: 111—112°C.
Analysis: Found C, 66.1%; H, 6.21%; N, 13.3%.
Calculated for $C_{23}H_{25}ClN_4O \cdot \frac{1}{2}H_2O$:
C, 66.1%; H, 6.27%; N, 13.4%.

EXAMPLE 5

2-(7-Chloro-4-quinolylamino)-N-[2-(dimethylamino)ethyl]-N-methylbenzamide

A solution of 10.05 grams (0.03 mole) of 2-(7-chloro-4-quinolylamino) benzoic acid hydrochloride in 60 millilitres of thionyl chloride was refluxed for two hours. Evaporation followed by the addition of dry benzene (2×50ml) and re-evaporation gave the acid chloride as a pinkish solid. This was added in portions to a stirred, ice-cooled solution of 3.1 grams (0.03 mole) of N,N,N¹-trimethylethylenediamine in 60 millilitres of chloroform with 120 millilitres of water and 31.8 grams of sodium carbonate. The mixture was stirred at room temperature overnight. The mixture was then filtered, the filtrate was separated and the chloroform layer was evaporated to give an oil. The oil was dissolved in ether and ethereal HCl added to precipitate the hydrochloride. This was dissolved in water and saturated sodium carbonate solution added to precipitate the free base as a gummy solid. Reconversion to the hydrochloride gave 8 grams of the title compound as its dihydrochloride dihydrate, m.p. 190—91°C.

Analysis: Found C, 53.2%; H, 5.29%; N, 12.0%;
$C_{21}H_{23}ClN_4O \cdot 2HCl \cdot 2H_2O$
requires: C, 53.2%; H, 5.74%; N, 11.8%.

EXAMPLE 6

N-(1-Benzyl-4-piperidyl)-2-(7-chloro-4-quinolylamino)benzamide

A solution of 10.05 grams (0.03 mole) of 2-(7-chloro-4-quinolylamino)benzoic acid hydrochloride in 60 millilitres of thionyl chloride was refluxed for two hours. Evaporation followed by the addition of dry benzene (20×50ml) and re-evaporation gave the acid chloride as a pinkish solid. This was added in portions to a stirred, ice-cooled solution of 5.71 grams (0.03 mole) of 4-amino-1-benzyl piperidine in 60 millilitres of chloroform with 120 millilitres of water and 31.8 grams of sodium carbonate and the mixture stirred at room temperature overnight. The mixture was then filtered, the filtrate was separated and the chloroform layer was evaporated to give a stick solid. This solid was triturated with ether to give the title compound, m.p. 171—72°C.

Analysis: Found: C, 70.5%; H, 5.83%; N, 11.5%; $C_{28}H_{27}ClN_4O \cdot \frac{1}{4}H_2O$
requires: C, 70.7%; H, 5.82%; N, 11.8%.

EXAMPLE 7

2-(7-Chloro-4-quinolylamino)-N-(2-dimethylaminoethyl)-N-ethyl benzamide

A solution of 10.5 grams (0.03 mole) of 2-(7-chloro-4-quinolylamino) benzoic acid hydrochloride in 60 millilitres of thionyl chloride was refluxed for two hours. Evaporation followed by the addition of dry benzene (2×50 ml) and re-evaporation gave the acid chloride as a pinkish solid. This was added in portions to a stirred ice-cooled solution of 3.5 grams (0.03 mole) of N,N-dimethyl-N-ethylethylenediamine in 60 millilitres of chloroform with 120 millilitres of water and 31.8 grams of sodium carbonate and the mixture stirred at room temperature overnight. The mixture was then filtered, the filtrate was separated and the chloroform layer was evaporated to give an oil. The oil was dissolved in ether and ethereal HCl added to precipitate 11.8 grams of the title compound as its dihydrochloride dihydrate, m.p. 175—180°C.

Analysis: Found: C, 51.8%; H, 5.73%; N, 10.9%;
$C_{22}H_{25}ClN_4 \cdot 2HCl \cdot 2H_2O$
requires: C, 52.5%; H, 6.17%; N, 11.1%.

EXAMPLE 8

2-(7-Chloro-4-quinolylamino)-N-(1-ethyl-4-piperidyl)benzamide

A solution of 15.1 grams (0.045 mole) of 2-(7-chloro-4-quinolylamino) benzoic acid hydrochloride in 90 millilitres of thionyl chloride was refluxed for two hours. Evaporation followed by the addition of dry benzene (2×75 ml) and re-evaporation

gave the acid chloride as a pinkish solid. This was added in portions to a stirred ice-cooled solution of 5.75 grams (0.045 mole) of 4-amino-N-ethyl piperidine in 90 millilitres of chloroform with 200 millilitres of water and 47.7 grams of sodium carbonate and the mixture was stirred at room temperature overnight. The mixture was then filtered, the filtrate was separated and the chloroform layer was evaporated to give a sticky solid which was triturated with ether to give a yellow solid. This was recrystallised from ethanol to give 4.7 grams of 2-(7-chloro-4-quinolylamino)-N-(1-ethyl-4-piperidyl)benzamide, m.p. 239—240°C.

Analysis: Found: C, 67.55%; H, 6.22%; N, 13.7%; $C_{23}H_{26}ClN_4O$
requires: C, 67.55%; H, 6.16%; N, 13.7%.

EXAMPLE 9

2-(7-Chloro-4-quinolylamino)-N-(2-diethylaminoethyl)-N-methyl benzamide

A solution of 10.05 grams (0.03 mole) of 2-(7-chloro-4-quinolylamino)benzoic acid hydrochloride in 60 millilitres of thionyl chloride was refluxed for two hours. Evaporation followed by the addition of dry benzene (2×50 ml) and re-evaporation gave the acid chloride as a pinkish solid. This was added in portions to a stirred ice-cooled solution of 3.91 grams (0.03 mole) of N,N-diethyl-N^1-methyl-ethylenediamine in 60 millilitres of chloroform with 120 millilitres of water and 31.8 grams of sodium carbonate and the mixture was stirred at room temperature overnight. The mixture was then filtered, the filtrate was separated and the chloroform layer was evaporated to give an oil. The oil was dissolved in ether and ethereal HCl added to precipitate the hydrochloride. This was dissolved in water and saturated sodium carbonate solution added to precipitate the free base as a gummy solid. Reconversion to the hydrochloride gave 9.0 grams of 2-(7-chloro-4-quinolylamino)-N-(2-diethylaminoethyl)-N-methyl benzamide dihydrochloride trihydrate, m.p. 90—95°C.

Analysis: Found: C, 51.2%; H, 6.42%; N, 10.3%;
$C_{23}H_{27}ClN_4O \cdot 2HCl \cdot 3H_2O$
requires: C, 51.35%; H, 6.56%; N, 10.4%.

EXAMPLE 10

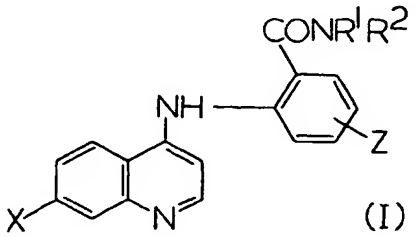
N-(1-n-Butyl-4-piperidyl)-2-(7-chloro-4-quinolylamino)benzamide

A solution of 10.05 grams (0.03 mole) of 2-(7-chloro-4-quinolylamino)benzoic acid hydrochloride in 60 millilitres of thionyl chloride was refluxed for two hours. Evaporation followed by the addition of dry benzene (2×50 ml) and re-evaporation gave the acid chloride as a pinkish solid. This was added in portions to a stirred ice-cooled solution of 4.7 grams (0.03 mole) of 4-amino-1-n-butyl piperidine in 60 millilitres of chloroform with 120 millilitres of water and 31.8 grams of sodium carbonate. The mixture was stirred at room temperature overnight. The mixture was then filtered, the filtrate was separated and the chloroform layer was evaporated to give a yellow solid which was triturated with ether. Recrystallisation from absolute alcohol gave 4.2 grams of N-(1-*n*-butyl-4-piperidyl)-2-(7-chloro-4-quinolylamino) benzamide, m.p. 231—32°C.

Analysis: Found: C, 69.0%; H, 6.82%; N, 12.7%; $C_{26}H_{29}ClN_4O$
requires: C, 68.7%; H, 6.69%; N, 12.8%.

WHAT WE CLAIM IS:—

1. A compound having the general formula



(I)

or an acid addition salt thereof, wherein X is a halogen atom or a trifluoromethyl group; Z is hydrogen, halogen, trifluoromethyl, lower alkyl, lower alkoxy, hydroxyl,

nitro, amino or mono- or di-alkyl substituted amino; R^1 represents hydrogen or lower alkyl; and R^2 represents [mono(lower alkyl)amino](lower alkyl), [di(lower alkyl)-amino](lower alkyl), piperidyl, 1-[ar-lower)alkyl]-piperidyl or 1-(lower alkyl)piperidyl or —NR^1R^2 represents [mono(lower alkyl(amino]piperidino or [di(lower alkyl)amino]-piperidino.

2. A compound as claimed in Claim 1, wherein R^2 represents [di(lower alkyl)-amino](lower alkyl) or 1-(lower alkyl)piperidyl or —NR^1R^2 represents [di(lower alkyl)-amino]piperidino.

3. A compound as claimed in Claim 1, wherein R^2 is [di(lower alkyl)amino]-(lower alkyl) whilst R^1 is lower alkyl or R^2 is 1-(lower alkyl)piperidyl.

4. A compound as claimed in Claim 1, wherein X is chlorine or bromine.

5. A compound as claimed in Claim 2 or 3, wherein X is chlorine or bromine.

6. A compound as claimed in Claim 1 or 4, wherein Z is hydrogen.

7. A compound as claimed in any one of Claims 2, 3 and 5, wherein Z is hydrogen.

8. 2 - (7 - Chloro - 4 - quinolylamino) - N - (1 - ethyl - 3 - piperidyl) benzamide or an acid addition salt thereof.

9. 2 - (7 - Chloro - 4 - quinolylamino) - N - (2 - diethylaminoethyl) - N - ethyl-benzamide or an acid addition salt thereof.

10. 2 - (7 - Chloro - 4 - quinolylamino) - N - (2 - diethylaminoethyl) - benzamide or an acid addition salt thereof.

11. 1 - [2 - (7 - Chloro - 4 - quinolylamino)benzoyl] - 4 - dimethylamino-piperidine or an acid addition salt thereof.

12. 2 - (7 - Chloro - 4 - quinolylamino) - N - (2 - dimethylaminoethyl) - N-methylbenzamide or an acid addition salt thereof.

13. N - (1 - Benzyl - 4 - piperidyl) - 2 - (7 - chloro - 4 - quinolylamino) - benzamide or an acid addition salt thereof.

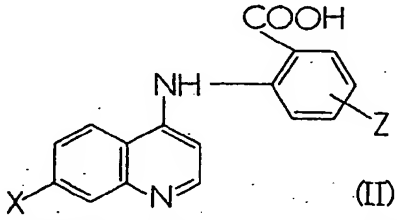
14. 2 - (7 - Chloro - 4 - quinolylamino) - N - (2 - dimethylaminoethyl) - N-ethylbenzamide or an acid addition salt thereof.

15. 2 - (7 - Chloro - 4 - quinolylamino) - N - (1 - ethyl - 4 - piperidyl) - benzamide or an acid addition salt thereof.

16. 2 - (7 - Chloro - 4 - quinolylamino) - N - (2 - diethylaminoethyl) - N-methylbenzamide or an acid addition salt thereof.

17. N - (1 - *n* - Butyl - 4 - piperidyl) - 2 - (7 - chloro - 4 - quinolylamino)-benzamide or an acid addition salt thereof.

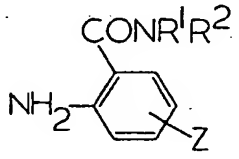
18. A process for the preparation of a compound claimed in Claim 1, wherein (a) a compound of the formula HNR^1R^2 (where R^1 and R^2 are as defined in Claim 1) or a corresponding compound with an activated amino group, is acylated with a compound of formula II



(II)

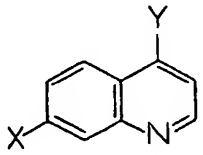
(wherein X and Z are as defined in Claim 1) or a corresponding compound with a protecting group, or a reactive derivative of the compound of formula II or its corresponding compound with a protecting group; or

(b) a compound of the formula (III)



(III)

(where R^1, R^2 and Z are as defined in Claim 1) or a corresponding compound with a protecting group, is reacted with a compound of formula IV



(IV)

(where X is as defined in Claim 1 and Y deontes a group or atom replaceable by nucleophilic attack by the compound of formula III); and, where necessary or if desired, a protecting group is removed and, if desired, a free base form of compound of formula I is converted into an acid addition salt form or an acid addition salt form of a compound of formula I is converted into the corresponding free base form.

19. A process as claimed in Claim 18, wherein R^2 is as defined in Claim 2.

20. A process as claimed in Claim 18, wherein R^2 is [di(lower alkyl)amino]-(lower alkyl) whilst R^1 is lower alkyl or R^2 is 1-(lower alkyl)piperidyl.

21. A process as claimed in Claim 18, wherein X is chlorine or bromine.

22. A process as claimed in Claim 19 or 20, wherein X is chlorine or bromine.

23. A process as claimed in Claim 18 or 21, wherein Z is hydrogen.

24. A process as claimed in any one of Claims 19, 20 or 22, wherein Z is hydrogen.

25. A process for the preparation of a compound claimed in Claim 2, carried out substantially as described in any one of Examples 1 to 3 herein.

26. A process for the preparation of a compound claimed in Claim 1, carried out substantially as described in any one of Examples 4 to 10 herein.

27. A compound claimed in Claim 1, whenever prepared by a process claimed in any one of Claims 18, 21, 23 and 26.

28. A compound claimed in Claim 2, whenever prepared by a process as claimed in any one of Claims 19, 20, 22, 24 and 25.

29. A pharmaceutical composition comprising a compound having formula I (as illustrated and defined in Claim 1) or a pharmaceutically acceptable acid addition salt thereof and a non-toxic carrier.

30. A composition as claimed in Claim 29, containing a compound claimed in any one of Claims 2, 3, 5, 7 to 10 and 28.

31. A composition as claimed in Claim 29, containing a compound claimed in any one of Claims 4, 6, 11 to 17 and 27.

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Printed for Her Majesty's Stationery Office, by the Courier Press, Leamington Spa, 1977
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.